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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
FISHER, ABIGAIL L	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,109	SEBEK ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12,14-18 and 22-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12,14-18 and 22-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments/Remarks filed on August 23 2010 is acknowledged. Claims 1, 13, and 19-21 were/stand cancelled. Claims 2-9, 12, 14, 16 and 18 were amended. Claims 22-35 were added. Claims 2-12, 14-18 and 22-35 are pending.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Modified Rejection Based on amendments in the reply filed on August 23 2010

Claims 9-11 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses oxygen absorbers such as Ageless®, Fresh Pax or

ATCO which meet the written description and enablement provisions of 35 USC 112, first paragraph. Specific oxygen absorbers are known in the art such as particulate iron, copper powder and zinc powder. However, claim(s) 9-11 and 30 is(are) directed to encompass any oxygen absorber. Furthermore, claims 10-11 and 30-31 further limit the oxygen absorbers to be specific groups such as self-activating, absorbers activated by a combination of activation processes, absorbers with necessity of activation, radiation-activated absorbers, microwaves-activated absorbers which only correspond in some undefined way to specifically instantly disclosed chemicals. These generic descriptions do not meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim. Note: MPEP 2163.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, (Fed. Cir. 1991), makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004), further supports this by stating that:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice.... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed absorbers regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Circ. 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, (Fed. Cir. 1991). In Fiddes v. Baird, 30 USPQ2d 1481, 1483, (Bd. Pat. App. & Int. 1993), claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 (Fed. Cir. 1997) held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Furthermore, to the extent that a functional description can meet the requirement for an adequate written description, it can do so only in accordance with PTO guidelines stating that the requirement can be met by disclosing "sufficiently detailed, relevant identifying characteristics," including "functional characteristics when coupled with a known or disclosed correlation between function and structure." Univ. of Rochester v. G.D. Searle, 68 USPQ2d 1424, 1432 (DC WNY 2003).

The specification fails to provide adequate written description for the instantly claimed oxygen absorbers. Specifically, the specification fails to provide a description of oxygen absorbers with sufficient specificity that one of ordinary skill in the art can

visualize or recognize the identity of the subject matter purportedly described. Furthermore, the specification fails to provide a description of self-activating absorbers or how these types of absorbers are different from those absorbers without the necessity of activation or any other of the instantly claimed oxygen absorbers.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Response to Arguments

Applicants argue that the real issue with respect to whether a written description exists is whether the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

Applicants' arguments filed August 23 2010 have been fully considered but they are not persuasive.

While the examiner agrees with applicants and that the issue is can one of ordinary skill immediately envisage the product. Additionally, the instant specification does not have to disclose what is commonly known. However, the examiner disagrees that these oxygen absorbers are well known. Waterman teaches two specific types of oxygen absorbers, humidity activated absorbers and UV activated absorbers. Therefore, the examiner agrees that these would be something one of ordinary skill in

the art would immediately envision. However for the other oxygen absorbers claimed, the examiner can find no description either in the specification or the art of what absorbers would fall within these categories. If these absorbers were as conventional as applicants believe, then description of these absorbers should be easy to find. The examiner has made attempts to search to find these "conventional" absorbers but can not find descriptions of these absorbers. Therefore, the rejection as it pertains to the above absorbers is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Modified Rejection Based on amendments in the reply filed on August 23 2010

Claims 2-3, 5-6, 8-12, 14-18, 22-23, 25-26 and 28-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenboom (NL9400940, cited in the Office action mailed on 5/21/10) in view of Mills et al. (US Patent No. 5686104, cited in the Office action mailed on 5/21/10) as evidenced by Singh et al. (US PGPUB No. 20030175338, cited in the Office action mailed on 5/21/10), Waterman (US PGPUB 20020132359, cited in the Office action mailed on 5/21/10), Townsend (in Development and Manufacture of Protein Pharmaceuticals, 2002, cited in the Office action mailed on 5/21/10) and Shriver et al. (The Manipulation of Air-Sensitive compounds, 1986, cited in the Office action mailed on 5/21/10).

Applicant Claims

The instant application claims a method for the stabilization of atorvastatin embedded in a gaseous mixture comprising stabilizing the atorvastatin in the form of

tablets or capsules in an amount from 1 to about 60% by weight of the total weight of the dosage form, packaged in a blister and maintaining a partial pressure of oxygen of at most 2 kPa wherein the partial pressure is achieved by packaging in a blister-forming machine by introducing a stream of inert gas into cavities in a lower shaped sheet with such intensity that the concept of the gas in the cavity exchanges at least once, wherein the stream of the inert gas introduced at a flow rate ranging form 180 to 3000 l/h. The instant application claims the purging chamber being located in a box having a permanently inert atmosphere.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Hoogenboom (utilizing the English Translation of the '940 document) is directed to method and arrangement for packaging discrete drugs and/or food stuffs such as tablets or capsules. The method as claimed (claim 1) is that tablets or capsules are delivered via a delivery tube which is provided with a delivery opening to the packaging such as a blister packaging with the characteristic that an inert gas is delivered also via the delivery tube in the direction of the discharge opening. The inert gas as claimed can be nitrogen (claim 2). When using a blister packaging the blister shell part is fed as a continuous strip whereby the delivery tube for the drug ends a the fill position location above the not yet closed blister shell part and whereby the gas delivery line ends immediately before a closing position and where the blister shell part is closed with a foil (claim 11). It is taught that various modification within the scope of the invention are possible. The essential element is that discrete drugs are surrounded by inert gas

during the delivery path so that in no case air is drawn into the packaging together with the products to be packaged (page 8, last paragraph).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Hoogenboom teach packaging drugs, Hoogenboom does not teach that the drug is atorvastatin. However, this deficiency is cured by Mills et al. as evidenced by Singh et al.

Mills et al. is directed to stable oral CI-981 (atorvastatin) formulation and a process of preparing. It is taught that the HMG-CoA reductase inhibitors are unstable in that they are susceptible to heat, moisture, low pH environment and light (column 2, lines 41-46). The formulation comprises the HMG-CoA reductase inhibitor stabilized by combining with at least one pharmaceutically acceptable alkaline earth metal salt such as calcium, magnesium and aluminum salts (column 3, lines 12-25). The composition comprises the active in about 1 to about 50% by weight of the composition. The stabilizer in an amount from about 5 to 75% of the composition. The composition additionally contains between about 5 and about 75% microcrystalline cellulose and between about 1 and about 80% lactose (column 3, lines 40-60).

Singh et al. teaches that atorvastatin is present in multiple amorphous and crystalline forms. The amorphous form is hygroscopic and unstable when exposed to oxygen. A more stable crystalline form was formed but it is highly susceptible to heat, moisture, a low pH environment and light (paragraph 0004 and 0005).

While Hoogenboom teach packaging drugs under inert gas, Hoogenboom do not teach utilizing oxygen absorbers to help reduce the partial pressure of oxygen. However, this deficiency is cured by Waterman.

Waterman is directed to a dispensing unit for oxygen-sensitive drugs. The dispensing unit provides for packaging means which dispenses a single dose of an oxygen-sensitive drug that does not permit the other dosage units from being exposed. The packaging includes a plurality of unit doses of an oxygen-sensitive drug, a lid and a blister. Each unit is individually encapsulated between the lid and the blister by means of a sealable laminate deposited on the lid; and an oxygen absorber incorporated into the laminate. The oxygen absorber is designed to remove a portion of the oxygen from the air surrounding the drug. Most preferably less than or equal to about 0.5% oxygen is in the air surrounding the drug for 2 years (paragraph 0009). The lid refers to a back or substrate. These include plastic or foil (paragraph 0022). It is taught that optionally lamination can be performed in an inert atmosphere (e.g. nitrogen blanket) (paragraph 0024). It is taught that the surface of the plastic blister significantly increases the potential for oxygen permeation. To mitigate this effect, blister packaging materials have evolved to minimize oxygen permeation. Modest reduction in oxygen levels are observed and maintained with foil-foil blisters. The invention of Waterman incorporates oxygen absorbers in a sufficient amount to remove at least a portion of the oxygen from the air to stop or retard the degradation process (paragraph 0026). One embodiment utilizes metal as the barrier material. The construction may consist of a foil (such as aluminum) with a coating or lamination of the oxygen absorbing material (paragraph

0029). Examples of oxygen absorbing material include iron, copper powder and zinc powder (paragraph 0030). It is taught that since the protection of the dosage form from environmental oxygen will require consumption of the oxygen absorbing material there will be a limited shelf-life. To increase the shelf-life with out increasing the thickness, complexity or cost, it can be desirable to include a secondary packaging part. Preferred secondary packaging consists of pouches containing one or more cards of blisters. Examples are oxygen absorbing sachet or cartridges such as Ageless (paragraph 0032). Examples of oxygen sensitive drugs include statins such as lovastatin and simvastatin (paragraph 0033).

Hoogenboom does not specify the flow rate of the inert gas. Hoogenboom does not specify utilizing a box with an inert atmosphere is utilized with packaging the drug. Hoogenboom does not specify utilizing a reduced pressure in the packaging. However, these deficiencies are cured by Townsend and Shriver et al.

Townsend teach that for oxygen-sensitive products, an inert gas such as nitrogen may be introduced to replace the air in the headspace of compounding and sterile holding tans as well as the final product containers. On the filling line this may be accomplished by flushing the vial with nitrogen from a delivery needle prior to, during and/or after solution filing. The gas pressure, flow rate, and purge time must be optimized during process development so as to meet the oxygen tension specification necessary to prevent oxidative degradation of the product (page 139, section 2.1.3.4, second paragraph).

Shriver et al. teach that an inert-atmosphere glove box provides a straightforward means of handing air-sensitive solids and liquids. The entire box is flushed with an inert gas after which samples may be manipulated in the inert atmosphere (page 45, second paragraph). It is taught that one method of replacing atmospheric gases with an inert gas is a pump and film. Such that the air inside is removed via a vacuum followed by replacement with the inert gas (page 48-49). When purging a vessel, the flow rate (L) necessary to maintain the partial pressure (P_0) of an atmospheric component at some desired partial pressure P inside the apparatus is given by the equation $L=-(AD_{1,2}/X)\ln(P/P_0)$ where A is the cross-sectional area of the tube through which the gas is issuing, X is the length of this tube and $D_{1,2}$ is the diffusion coefficient of the impurity gas 1 in the inert gas 2. One flow rate taught is 50 ml/min. However it is stated that experience teaches that far larger flow rates are required; something on the order of several liters per minute (page 9).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hoogenboom, Mills et al., Waterman, Townsend and Shriver et al. and utilize blister packaging which is formed under an inert atmosphere with oxygen absorbers in order to stabilize a pharmaceutical composition comprising atorvastatin. One of ordinary skill in the art would have been motivated to utilize blister packaging, an inert atmosphere and oxygen absorbers as atorvastatin is known to be air sensitive as taught by Mills et al. and Singh et al. Hoogenboom and Waterman teach that ways of stabilizing air sensitive compounds is to utilize blister

packaging with an inert atmosphere and oxygen absorbers. Therefore in order to increase the stability of pharmaceutical formulations comprising air sensitive compounds like atorvastatin, one of ordinary skill in the art would have been motivated to decrease the air in the head space by exchanging the air with a heavier inert gas such as nitrogen as well as including oxygen absorbers in the packaging to decrease the oxygen levels.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hoogenboom, Mills et al., Waterman, Townsend and Shriver et al. and manipulate the flow rate of the inert gas. One of ordinary skill in the art would have been motivated to manipulate the flow rate as Townsend teaches that the gas pressure, flow rate, and purge time must be optimized during process development so as to meet the oxygen tension specification necessary to prevent oxidative degradation of the product. Since Shriver et al. teach a formula for the flow rate required for a particular partial pressure and base don the teachings of Townsend, the flow rate is something one of ordinary skill in the art would routinely optimize. The flow rate is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable

ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hoogenboom, Mills et al., Waterman, Townsend and Shriver et al. and utilize a glove box when packaging air sensitive compounds. One of ordinary skill in the art would have been motivated to utilize a glove box as Shriver et al. teach that manipulation of air sensitive compounds is routinely conducted in a glove box where an inert atmosphere can be maintained. Since atorvastatin is known to be air sensitive, it would have been obvious to one of ordinary skill in the art to perform all packaging steps in a glove box where an inert atmosphere can be maintained, thereby reducing the air contamination.

Regarding the claimed pressure, one method of purging taught is to first apply a vacuum to help remove the atmospheric air followed by purging with an inert gas. Therefore, it would have been obvious to one of ordinary skill in the art to first apply a vacuum followed by purging with an inert gas atmosphere in order to aid in the removal of the atmospheric contaminant as taught by Shriver et al.

Regarding claim 5, there are two forms of atorvastatin crystalline and amorphous. Since Mills et al. teach utilizing the free acid form as well as the salt form, it would have been obvious to one of ordinary skill in the art to utilize either the crystalline or the amorphous form. Since the methods of protection taught by Hoogenboom and Waterman are designed to protect air sensitive compounds such as amorphous

atorvastatin, one of ordinary skill in the art would have been motivated to utilize this form of atorvastatin in combination with blister packs comprising inert gas and oxygen absorbers in order to increase the stability of the atorvastatin.

Regarding claim 6, Hoogenboom teaches utilizing a blister but is silent as to the material making up the blister except to state foil. Waterman teaches that material making the substrate can be plastic or foil. Types of blisters taught include foil-foil blisters and an example of foil taught by Waterman is aluminum. Therefore, one of ordinary skill in the art would have been motivated to utilize an Al-Al blister as this type of blister is taught has having virtually no permeability to oxygen. One of ordinary skill in the art would have been motivated to utilize an Al-Al blister in order to decrease the oxygen present in packaging as taught by Waterman.

Regarding the claimed partial pressure, the cited art does not explicitly state the partial pressure of the oxygen. However, the use of an inert gas and oxygen absorbers (which are the methods instantly claimed at achieving the claimed partial pressure) would have been obvious to one of ordinary skill in the art. Furthermore, Waterman teaches that the percentage of oxygen present is about 0.5% or less. Therefore, very small amounts of oxygen are taught by the cited prior art. The amount of a oxygen absorbers in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best

achieve the desired results. It would have been obvious to one of ordinary skill in the art to manipulate the amount of oxygen absorber utilized in order to manipulate the amount of resulting oxygen present in the blister packaging. Waterman teaches that oxygen absorbers can be incorporated in the packaging as well as in the packaging that holds the blisters (secondary packaging). Therefore, it would have been obvious to one of ordinary skill to manipulate the number of oxygen absorbers utilized depending on the desired low level of oxygen. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenboom in view of Mills et al. as evidenced by Singh et al., Waterman, Townsend and Shriver et al. and in further view of Joshi (US Patent No. 5180589, cited in the Office action mailed on 5/21/10).

Applicant Claims

The instant application claims that the atorvastatin is in a mixture containing solid magnesium oxide.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Hoogenboom, Mills et al., Waterman, Townsend and Shiver et al. are set forth above. Hoogenboom teach a method of packaging pharmaceuticals under inert gas in order to prevent exposure to air. Mills et al. is directed to pharmaceutical compositions comprising atorvastatin. The compositions utilize an alkaline salt such as calcium, magnesium or aluminum in order to increase the stability of the composition. Waterman teach utilizing oxygen absorbers in order to help stabilize oxygen sensitive compounds.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Hoogenboom and Mills et al. do not teach the incorporation of magnesium oxide. However, this deficiency is cured by Joshi.

Joshi is directed to pravastatin pharmaceutical compositions. Pravastatin is compound which is HMG-CoA reductase inhibitor (as is atorvastatin). The composition comprises a basifying agent which raises th pH of an aqueous dispersion of the composition in order to increase stability. Examples of basifying agents include magnesium oxide, aluminum oxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, etc. (columns 1-2, lines 60-68 and 1-6).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hoogenboom, Mills et al., Waterman, Townsend, Shriver et al. and Joshi and utilize magnesium oxide as the basifying agent. One of ordinary skill in the art would have been motivated to utilize magnesium oxide as Mills et al. teach utilizing magnesium salts as basic supplements for stabilizing atorvastatin and Joshi teaches that other magnesium salt basifying agents for use with a similar statin includes magnesium oxide. It would have been obvious to one of ordinary skill in the art to try basifying agents known to be utilized with statins as a person with ordinary skill has good reason to pursue known options within his or her technical grasp. **Note: MPEP 2141 [R-6]** *KSR International CO. v. Teleflex Inc.* 82 USPQ 2d 1385 (Supreme Court 2007).

Regarding the claimed amount of drug, magnesium oxide, lactose and microcrystalline cellulose, Mills et al. teach an amount overlap that instantly claimed. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. See MPEP 2144.05 [R-5]

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 7 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenboom in view of Mills et al. as evidenced by Singh et al., Waterman,

Townsend and Shriver et al. and in further view of Pilchik (Pharmaceutical Technology, 2000, cited in the Office action mailed on 5/21/10).

Applicant Claims

The instant application claims that the drug is packaged in a polypropylene blister which is further enveloped in an Al-Al pouch.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Hoogenboom, Mills et al., Waterman, Townsend and Shriver et al. are set forth above. Hoogenboom teach a method of packaging pharmaceuticals under inert gas in order to prevent exposure to air. The packaging material is a blister. Mills et al. is directed to pharmaceutical compositions comprising atorvastatin. The compositions utilize an alkaline salt such as calcium, magnesium or aluminum in order to increase the stability of the composition. Waterman teach utilizing oxygen absorbers in order to help stabilize oxygen sensitive compounds. It is taught to package pharmaceutical compositions in blister packaging made of plastic or foil. It is taught that the blisters can be further packaged in pouches made of plastic or foil (paragraph 0032). It is taught that a general review of blister packaging may be found in Pharm. Teach 2000 (paragraph 0024).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Hoogenboom and Waterman do not teach that the blister is made of polypropylene. However, this deficiency is cured by Pilchik.

Pilchik, which is the Pharm. Teach reference referred to by Waterman, teaches that plastics which can be utilized to form the films include polypropylene. The advantages of utilizing polypropylene include recyclability, no release of toxins during incineration and good moisture-barrier properties (page 6, paragraph 5).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Hoogenboom, Mills et al., Waterman and Pilchik and utilize polypropylene as the plastic material for forming the blisters. One of ordinary skill in the art would have been motivated to utilize polypropylene for the advantages taught by Pilchik such as recyclability and good moisture barrier properties. One of ordinary skill in the art would have been motivated to place the polypropylene blister in an aluminum pouch as Waterman teach that the placement of the blisters in the pouch allow for greater stability (shelf-life). Therefore, one of ordinary skill in the art would have been motivated to place the blister in an aluminum (foil) pouch in order to extend the shelf life of the pharmaceutical composition.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2-6, 8-12, 14-18, 22-26 and 28-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pflaum et al. (WO 0193859, cited on PTO form 1449) as evidenced by Singh et al. and in view of Waterman, Townsend and Shriver et al.

Applicant Claims

The instant application claims a method for the stabilization of atorvastatin embedded in a gaseous mixture comprising stabilizing the atorvastatin in the form of tablets or capsules in an amount from 1 to about 60% by weight of the total weight of the dosage form, packaged in a blister and maintaining a partial pressure of oxygen of at most 2 kPa wherein the partial pressure is achieved by packaging in a blister-forming machine by introducing a stream of inert gas into cavities in a lower shaped sheet with such intensity that the concept of the gas in the cavity exchanges at least once, wherein the stream of the inert gas introduced at a flow rate ranging form 180 to 3000 l/h. The instant application claims the purging chamber being located in a box having a permanently inert atmosphere.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Pflaum et al. is directed to stable pharmaceutical product and formulation. The formulations contain as an active substance an HMG-CoA reductase inhibitor (page 3, lines 26-28). The pharmaceutical formulation unit usually is a solid pharmaceutical dosage form such as a compressed tablet or capsule (page 8, lines 33-35). The tablets or capsules may be placed into appropriate dosage form containers to form the pharmaceutical package such as blister packages (page 9, lines 1-3). The formulation

contains a buffering agent or a basifying agent in amount of 20% or less based on the total weight of the pharmaceutical formulation (page 12, lines 4-6). Examples of buffering or basifying agents include metal oxides such as magnesium oxide (page 12, line 35). The formulation can comprise additional excipients such as microcrystalline cellulose and lactose (page 16, lines 8-20). HMG-CoA reductase inhibitors claimed include atorvastatin and pharmaceutically acceptable salts thereof (claim 17).

Singh et al. teaches that atorvastatin is present in multiple amorphous and crystalline forms. The amorphous form is hygroscopic and unstable when exposed to oxygen. A more stable crystalline form was formed but it is highly susceptible to heat, moisture, a low pH environment and light (paragraph 0004 and 0005).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Pflaum et al. teach utilizing blister packaging, Pflaum et al. do not teach utilizing oxygen absorbers to help reduce the partial pressure of oxygen or a nitrogen blanket. However, this deficiency is cured by Waterman.

Waterman is directed to a dispensing unit for oxygen-sensitive drugs. The dispensing unit provides for packaging means which dispenses a single dose of an oxygen-sensitive drug that does not permit the other dosage units from being exposed. The packaging includes a plurality of unit doses of an oxygen-sensitive drug, a lid and a blister. Each unit is individually encapsulated between the lid and the blister by means of a sealable laminate deposited on the lid; and an oxygen absorber incorporated into the laminate. The oxygen absorber is designed to remove a portion of the oxygen from the air surrounding the drug. Most preferably less than or equal to about 0.5% oxygen

is in the air surrounding the drug for 2 years (paragraph 0009). The lid refers to a back or substrate. These include plastic or foil (paragraph 0022). It is taught that optionally lamination can be performed in an inert atmosphere (e.g. nitrogen blanket) (paragraph 0024). It is taught that the surface area of plastic blister significantly increase the potential for oxygen permeation. To mitigate this effect, blister packaging materials have evolved to minimize oxygen permeation. Modest reduction in oxygen levels are observed and maintained with foil-foil blisters. The invention of Waterman incorporates oxygen absorbers in a sufficient amount to remove at least a portion of the oxygen from the air to stop or retard the degradation process (paragraph 0026). One embodiment utilizes metal as the barrier material. The construction may consist of a foil (such as aluminum) with a coating or lamination of the oxygen absorbing material (paragraph 0029). Examples of oxygen absorbing material include iron, copper powder and zinc powder (paragraph 0030). It is taught that since the protection of the dosage form from environmental oxygen will require consumption of the oxygen absorbing material there will be a limited shelf-life. To increase the shelf-life with out increasing the thickness, complexity or cost, it can be desirable to include a secondary packaging part. Preferred secondary packaging consists of pouches containing one or more cards of blisters. Examples are oxygen absorbing sachet or cartridges such as Ageless (paragraph 0032). Examples of oxygen sensitive drugs include statins such as lovastatin and simvastatin (paragraph 0033).

Pflaum et al. does not specify the flow rate of the inert gas. Pflaum et al. does not specify utilizing a box with an inert atmosphere is utilized with packaging the drug.

Pflaum et al. does not specify utilizing a reduced pressure in the packaging. However, these deficiencies are cured by Townsend and Shriver et al.

Townsend teach that for oxygen-sensitive products, an inert gas such as nitrogen may be introduced to replace the air in the headspace of compounding and sterile holding tans as well as the final product containers. On the filling line this may be accomplished by flushing the vial with nitrogen from a delivery need prior to, during and/or after solution filing. The gas pressure, flow rate, and purge time must be optimized during process development so as to meet the oxygen tension specification necessary to prevent oxidative degradation of the product (page 139, section 2.1.3.4, second paragraph).

Shriver et al. teach that an inert-atmosphere glove box provides a straightforward means of handing air-sensitive solids and liquids. The entire box is flushed with an inert gas after which samples may be manipulated in the inert atmosphere (page 45, second paragraph). It is taught that one method of replacing atmospheric gases with an inert gas is a pump and film. Such that the air inside is removed via a vacuum followed by replacement with the inert gas (page 48-49). When purging a vessel, the flow rate (L) necessary to maintain the partial pressure (P_0) of an atmospheric component at some desired partial pressure P inside the apparatus is given by the equation $L=-(AD_{1.2}/X)\ln(P/P_0)$ where A is the cross-sectional area of the tube through which the gas is issuing, X is the length of this tube and $D_{1.2}$ is the diffusion coefficient of the impurity gas 1 in the inert gas 2 . One flow rate taught is 50 ml/min. However it is stated that

experience teaches that far larger flow rates are required; something on the order of several liters per minute (page 9).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Pflaum et al., Waterman, Townsend and Shriver et al. and utilize blister packaging which is formed under an inert atmosphere with oxygen absorbers in order to stabilize a pharmaceutical composition comprising atorvastatin. One of ordinary skill in the art would have been motivated to utilize blister packaging, an inert atmosphere and oxygen absorbers as atorvastatin is known to be air sensitive as taught by Pflaum et al. and Singh et al. Waterman teach that ways of stabilizing air sensitive compounds is to utilize blister packaging with an inert atmosphere (nitrogen blanket) and oxygen absorbers. Therefore in order to increase the stability of pharmaceutical formulations comprising air sensitive compounds like atorvastatin, one of ordinary skill in the art would have been motivated to decrease the air in the head space by exchanging the air with a heavier inert gas such as nitrogen as well as including oxygen absorbers in the packaging to decrease the oxygen levels.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Pflaum et al., Waterman, Townsend and Shriver et al. and manipulate the flow rate of the inert gas. One of ordinary skill in the art would have been motivated to manipulate the flow rate as Townsend teaches that the gas pressure, flow rate, and purge time must be optimized during process development so as to meet the oxygen tension specification necessary to prevent

oxidative degradation of the product. Since Shriver et al. teach a formula for the flow rate required for a particular partial pressure and base don the teachings of Townsend, the flow rate is something one of ordinary skill in the art would routinely optimize. The flow rate is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Pflaum et al., Waterman, Townsend and Shriver et al. and utilize a glove box when packaging air sensitive compounds. One of ordinary skill in the art would have been motivated to utilize a glove box as Shriver et al. teach that manipulation of air sensitive compounds is routinely conducted in a glove box where an inert atmosphere can be maintained. Since atorvastatin is known to be air sensitive, it would have been obvious to one of ordinary skill in the art to perform all packaging steps in a glove box where an inert atmosphere can be maintained, thereby reducing the air contamination.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Pflaum et al., Waterman, Townsend and Shriver et al. and utilize magnesium oxide as the basifying agent. One of ordinary skill in the art would have been motivated to utilize magnesium oxide as it is specific basifying agent taught by Pflaum et al. It would have been obvious to one of ordinary skill in the art to try any of the specifically taught basifying agents as a person with ordinary skill has good reason to pursue known options within his or her technical grasp. **Note: MPEP 2141 [R-6]** *KSR International CO. v. Teleflex Inc.* 82 USPQ 2d 1385 (Supreme Court 2007).

Regarding claim 5, there are two forms of atorvastatin crystalline and amorphous. Since Pflaum et al. teach utilizing the free acid form as well as the salt form, it would have been obvious to one of ordinary skill in the art to utilize either the crystalline or the amorphous form. Since the methods of protection taught by Waterman are designed to protect air sensitive compounds such as amorphous atorvastatin, one of ordinary skill in the art would have been motivated to utilize this form of atorvastatin in combination with blister packs comprising inert gas and oxygen absorbers in order to increase the stability of the atorvastatin.

Regarding claim 6, Pflaum et al. teaches utilizing a blister but is silent as to the material making up the blister. Waterman teaches that material making the substrata (of a blister) can be plastic or foil. Types of blisters taught include foil-foil blisters and an example of foil taught by Waterman is aluminum. Therefore, one of ordinary skill in the art would have been motivated to utilize an Al-Al blister as this type of blister is taught

has having virtually no permeability to oxygen. One of ordinary skill in the art would have been motivated to utilize an Al-Al blister in order to decrease the oxygen present in packaging as taught by Waterman.

Regarding the claimed partial pressure, the cited art does not explicitly state the partial pressure of the oxygen. However, the use of an inert gas and oxygen absorbers (which are the methods instantly claimed at achieving the claimed partial pressure) would have been obvious to one of ordinary skill in the art. Furthermore, Waterman teaches that the percentage of oxygen present is about 0.5% or less. Therefore, very small amounts of oxygen are taught by the cited prior art. The amount of a oxygen absorbers in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art to manipulate the amount of oxygen absorber utilized in order to manipulate the amount of resulting oxygen present in the blister packaging. Waterman teaches that oxygen absorbers can be incorporated in the packaging as well as in the packaging that holds the blisters (secondary packaging). Therefore, it would have been obvious to one of ordinary skill to manipulate the number of oxygen absorbers utilized depending on the desired low level of oxygen. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine

optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

Regarding the claimed amount of magnesium oxide, Pflaum et al. teach an amount overlap that instantly claimed. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. See MPEP 2144.05 [R-5]

Regarding the claimed pressure, one method of purging taught is to first apply a vacuum to help remove the atmospheric air followed by purging with an inert gas. Therefore, it would have been obvious to one of ordinary skill in the art to first apply a vacuum followed by purging with an inert gas atmosphere in order to aid in the removal of the atmospheric contaminant as taught by Shriver et al.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 7 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pflaum et al. as evidenced by Singh et al. in view of Waterman, Townsend and Shriver et al. and in further view of Pilchik (Pharmaceutical Technology, 2000, cited in the Office action mailed on 5/21/10).

Applicant Claims

The instant application claims that the drug is packaged in a polypropylene blister which is further enveloped in an Al-Al pouch.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Pflaum et al. and Waterman are set forth above. Pflaum et al. teach pharmaceutical compositions comprising HMG-CoA reductase inhibitors and basifying agents. Microcrystalline cellulose and lactose are taught as suitable excipients. Packaging in a blister is taught. Waterman teach utilizing oxygen absorbers in order to help stabilize oxygen sensitive compounds. It is taught to package pharmaceutical compositions in blister packaging made of plastic or foil. It is taught that the blisters can be further packaged in pouches made of plastic or foil (paragraph 0032). It is taught that a general review of blister packaging may be found in Pharm. Teach 2000 (paragraph 0024).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Pflaum et al. and Waterman do not teach that the blister is made of polypropylene. However, this deficiency is cured by Pilchik.

Pilchik, which is the Pharm. Teach reference referred to by Waterman, teaches that plastics which can be utilized to form the films include polypropylene. The advantages of utilizing polypropylene include recyclability, no release of toxins during incineration and good moisture-barrier properties (page 6, paragraph 5).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Pflaum et al., Waterman, Townsend and Shriver et al. and Pilchik and utilize polypropylene as the plastic material for forming the blisters. One of ordinary skill in the art would have been motivated to utilize polypropylene for the advantages taught by Pilchik such as recyclability and good moisture barrier properties. One of ordinary skill in the art would have been motivated to place the polypropylene blister in an aluminum pouch as Waterman teach that the placement of the blisters in the pouch allow for greater stability (shelf-life). Therefore, one of ordinary skill in the art would have been motivated to place the blister in an aluminum (foil) pouch in order to extend the shelf life of the pharmaceutical composition.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that (1) Pflaum discloses the use of the components to prevent the lowering of the pH by CO_2 in the atmosphere. It is argued that the amorphous atorvastin is unstable and the presently claimed invention solves a problem previously existing in the art. Applicants argue that (2) the examiner relies on impermissible

hindsight to form the rejection. It is argued that applicants are aware of the Office's often utilized rebuttal to the argument of impermissible hindsight. It is argued that the examiner has not provided any reasonable basis to conclude that the knowledge pieced together using Applicants' disclosure could have been pieced together in the absence of the disclosure. Applicants argue that (3) at best the combined disclosures could be taken as an invention to experiment or obvious to try. This does not constitute obviousness.

Applicants' arguments filed October 23 2010 have been fully considered but they are not persuasive.

Regarding applicants' augments, Hoogenboom expressly teaches that the essential element is that discrete drugs are surrounded by inert gas during the delivery path so that in no case air is drawn into the packaging together with the products to be packaged. Therefore Hoogenboom teaches packaging drugs under an inert gas. The question to be asked is, would it have been obvious to one of ordinary skill in the art to utilize atvorstatin in packaging under an inert gas with oxygen absorbers. The examiner maintains that the art suggests that this would have been obvious. Mills et al. teach that HMG-COA reductase inhibitors are unstable and Singh et al. expressly teaches that the amorphous form of atorvastatin is hydroscopic and unstable when exposed to oxygen. Therefore, when packaging atvorstatin, one of ordinary skill would be readily apprised based on the teachings of the prior art that care would need to be taken when handing atvorstatin (especially in amorphous form) and would have been motivated to limit exposure of the drug to moisture and oxygen. This provides the motivation to one of

ordinary skill in the art to package the drug in the presence of oxygen absorbers and under an inert atmosphere. Therefore, the art provides the motivation, not applicants' disclosure. Regarding the rejection over Pflaum et al., firstly the presence of additional agents to help stabilize atvorstatin are not excluded from the instantly claimed dosage form. Pflaum et al. teach utilizing blister packaging to package atvorstatin. The question is would it have been obvious to utilize a nitrogen blanket and oxygen absorbers. The examiner maintains that based on the teachings of the prior art (specifically Waterman, Singh et al.) it would have been. Atvorstatin is known to be unstable to oxygen therefore it would have been desirable, based on the teachings of the prior art, to limit exposure of the drug to oxygen.

Regarding applicants' third argument, the examiner assumes applicants are referring to the examiners statements about the partial pressure of oxygen and flow rate (applicants did not specifically point out which sections of the Office action possess the language referred to by applicants). Waterman and Hoogenboom both talk about utilizing a nitrogen blanket (or inert gas) to replace the air in the blister package with nitrogen. However, both are silent to the flow rate. Clearly there is some flow rate. The examiner's statements were that the flow rate would have been obvious to optimize. This is supported by Townsend which teaches that gas pressure, flow rate and purge time are those which are optimized during process development. Therefore, the art recognizes this as something to be optimized. Furthermore, applicants have not demonstrated the criticality of the instantly claimed flow rate. Regarding the partial pressure, since atvorstatin is unstable to oxygen exposure, one of ordinary skill in the

art would have desired to eliminate all of the oxygen (therefore a 0 partial pressure). That is why the examiner stated that the amount of oxygen absorber and subsequently the partial pressure of oxygen would be optimized as one of ordinary skill would manipulate the packaging material to achieve as low of a partial pressure of oxygen as possible. Furthermore, the use of oxygen absorbers and nitrogen blanket are obvious based on the teachings of the prior art. These are the two methods utilized by the instant invention to achieve the instantly claimed partial pressure. Therefore, since these two methods are suggested by the prior art, the partial pressure would reasonably be expected to be present. The examiner maintains that there is a reasonable expectation of success as the art recognizes that atvorstatin is unstable upon exposure to moisture and oxygen. Therefore, one of ordinary skill in the art would have been motivated to protect the dosage form from these elements. Ways to protect the dosage form from these elements is by utilizing a nitrogen blanket and oxygen absorbers. Therefore, the instantly claimed method is obvious based on the teachings of the prior art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Abigail Fisher
Examiner
Art Unit 1616

AF

/Mina Haghighatian/
Primary Examiner, Art Unit 1616